

Viral hepatitis C

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ABSTRACT

Hepatitis C is caused by the hepatitis C virus (HCV) infection. According to World Health Organization data, 3% of the world population (approximately 170 million people) is infected with HCV; in Poland there are over 700,000. Over 70% of those infected manifest no symptoms in the acute phase of the disease, and in about 70–80% the acute phase progresses into a chronic form. Patients with symptoms in the acute phase of HCV infection most commonly present with unspecific signs and symptoms that may develop in other viral liver infections, e.g. malaise, fatigue, abdominal pain, mild hepato- and splenomegaly and arthralgia. These symptoms usually persist for 2 to 12 weeks. In the chronic phase a subset of patients complain of malaise, nausea, abdominal pain and itching. With time, chronic hepatitis C may develop into liver cirrhosis. The basic diagnostic methods in HCV infection involve determination of anti-HCV antibodies using the ELISA immunoassay and examination of HCV-RNA with the RT-PCR method. The current treatment of HCV infection involves administration of pegylated interferon α and ribavirin over a period of 48 weeks in HCV-1 genotype infection, and 24 weeks for HCV-2 and 3 genotypes. Effectiveness of therapy depends on the HCV genotype. HCV elimination can be achieved in 78% of patients with HCV-2 and 3 genotypes, and in 55% of patients with HCV-1 genotype.

INTRODUCTION Viral hepatitis caused by the hepatitis C virus (HCV) is now one of the most serious health problems. This results from spreading of this virus worldwide, various routes of its transmission and lack of truly efficient therapy. In about 80% of patients acute hepatitis C progresses into a chronic disease, chronic hepatitis C after years of infection leads to a series of complications that mark this disease, and then quite commonly to death.¹

The HCV was discovered in the USA in 1989.² It is a flavivirus containing a single RNA strand made up of approximately 10,000 nucleotides and encapsulated by an external lipid envelope. The diameter of the virus is about 50–60 nm.¹ The HCV is a highly heterogenous virus. There are at least 6 genotypes of the virus, marked from 1 to 6, and more than 50 subtypes marked with letters (e.g. 1a, 1b, 2a, 2b). Nucleotide sequences of the individual virus genotypes differ by approximately 31–34%, and by about 20–23% in the group of subtypes.³ Because of the large genome variability and frequent mutations,

a population of HCV in an infected patient is heterogeneous, and helps the virus to survive the host immune system defense mechanisms. As a result, the HCV with altered features is not eliminated from the body by anti-HCV antibodies, which can only prove the infection (like an HIV infection).¹

Epidemiological data According to World Health Organization data, 3% of the human population, i.e. approximately 170 million people, is infected with HCV. The prevalence of HCV chronic infection is 0.1% to 26% and varies in different regions.^{1,4} The prevalence of HCV infection in Eastern Europe is about 0.7–4.9%.² In Poland, the percentage of people in whom anti-HCV antibodies have been detected is about 1.4%, which amounts to approximately 500,000 people. According to the most recent data, this number is underestimated, and the presumed number of the infected persons is over 750,000. According to data from the National Department of Hygiene and from the Chief Sanitary Inspectorate, in recent

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times approximately 2000 people every year are infected with HCV in Poland.^{3,5}

There are 6 types and numerous subtypes of HCV. Genotype 1 is the most common – it is present 40–80% of all patients with HCV chronic infection. Genotype 1 prevails in the USA, but in Europe and Japan genotypes 2 and 3 are more common. Genotype 4 is the most common genotype in Egypt and the Middle East. In southern Africa genotype 5 is most prevalent, for Hong Kong and other countries of south-eastern Asia it is genotype 6; genotypes 4, 5 and 6 are rarely found outside of those African or Asian regions. In Poland, about 80% of patients are infected with genotype 1b virus.^{6,7}

Routes of transmission of hepatitis C Hepatitis C may spread through blood and blood products, sexual contact, and vertically. There are also “occasional” infections, which account for as many as 40% of all chronic hepatitis C cases. They can be diagnosed as such when the source of infection is unknown.

Blood infection may result from a blood transfusion or an organ transplant, it may occur during invasive diagnostic procedures (e.g. organ biopsies, endoscopic examination). There are approximately 10^5 to 10^7 viral particles in 1 ml of blood of an infected patient with the chronic form of the disease, and up to 10^9 /ml in about 15% of patients. The quantity of the virus in body fluids and tissues is much lower.³ A high incidence of infection in Poland is reported in the drug addict population who use intravenous narcotics; this is approximately 57–90% of cases. Drug users infected with HIV more frequently contract HCV. There are 2 groups of patients particularly prone to the infection: hemophiliacs and patients receiving hemodialysis. It is estimated that approximately 50–90% of hemophiliacs worldwide are infected with HCV.³ This is caused by numerous blood transfusions and blood product infusions, however, the introduction of new diagnostic methods in blood therapy has significantly lowered the risk of transmission.

The incidence of anti-HCV antibodies in the blood of patients receiving hemodialysis depends on the duration of dialysis and grows with the frequency of the procedure. It is estimated that the incidence of HCV infections in this group is about 10–20% worldwide, and in Poland it reaches 30–58%.³

When a donor of an organ transplant is an HCV-infected person, a transmission of the virus occurs in 50% of patients. When immunotherapy is included into the treatment of a patient infected with HCV following transplantation, a chronic or fulminant form of hepatitis C frequently occurs.¹

The infection can also be acquired through an occupational exposure to blood, basically in health care workers, but also policemen, city guards, and penitentiary workers.

The HCV infection can also be the result of perinatal exposure. The routes of transmission from

a mother to a child and the timing of the contraction are still unclear. It is not known whether contracting the disease could occur during pregnancy, at birth, after delivery or while breastfeeding. There is no evidence as yet for transmission through mother's milk. At present, the ways to protect a child against HCV infection are unknown. More commonly, the infection of a child takes place in acute hepatitis C in the third trimester of pregnancy, and when accompanied by HIV infection. It should be highlighted that just after birth the anti-HCV antibodies can be detected in child's blood (persisting even up to 1.5 years), passively transmitted from the mother; this phenomenon is of no significance in pathogenesis of HCV infection.⁸

Sexual transmission as a route of HCV infection is estimated to occur in 2 to 27% of patients, depending on the study; on average no more than 15% of such cases are approved as most probable. The rate of infected individuals correlates with the number of sexual encounters, with prostitutes and intravenous drug users being the most commonly affected. Variable epidemiological data are reported for homosexuals.³ Similarly, inconsistent data about the intrafamilial transmission have been published. It is estimated that the prevalence of HCV infection is 6–23% among spouses.

History and clinical presentation of hepatitis C

The incubation period of HCV is usually 15–150 days from the moment of exposure, with an average of 40–50 days. The antibodies can be detected 4 weeks from the time of contraction at the earliest, but most commonly this period exceeds 10 weeks. No antibodies are detected in about 7% of patients. In more than 70% of cases, patients exhibit no signs and symptoms. Non-characteristic signs or symptoms are reported in 10–30% of cases, and they involve mild stomach discomfort, sometimes flu-like symptoms, myalgia, arthralgia and low-degree fever. Jaundice and liver enlargement are rare and occur in approximately 1/3 of patients. Serum alanine aminotransferase (ALT) activity is usually elevated and may be 10 times normal. A fulminant hepatitis C is very infrequently reported in an acute phase. However, in 70–80% of patients there is a progression into a chronic process. The infection with HCV along with the confirmed lack of HCV-RNA in the liver tissue after infection does not necessarily mean that such an individual will not be re-infected.^{1,3}

In the course of long-standing chronic hepatitis, gradual damage to the liver develops. Basically, most individuals with chronic hepatitis do not exhibit any symptoms for a long time. The only sign of the disease may be fatigue. Dyspepsia or itching appear rarely. Serum ALT levels are normal or slightly elevated. Infrequently, serum γ -glutamyl transpeptidase, alkaline phosphatase and bilirubin levels are slightly increased. After 20 years liver cirrhosis develops and its typical

TABLE 1 The progress of necrotic inflammatory process activity (G) in portal and periportal areas and in the lobules, scored from 0 to 4 according to Batts-Ludwig¹⁷

0	inflammatory lesions limited to the portal area, no piecemeal necrosis or characteristics of lobular inflammation (a presentation which corresponds to <i>hepatitis chronica persistens</i> in classic terminology)
1	periportal inflammatory infiltration, focal piecemeal necrosis and lobular inflammatory lesions of a minor degree (<i>hepatitis chronica activa minimalis</i>)
2	periportal inflammatory, focal piecemeal necrosis around some portal areas and intralobular inflammatory lesions of a minor degree (<i>hepatitis chronica activa minoris gradus</i>)
3	periportal inflammatory infiltration, piecemeal necrosis around all portal areas and lobular inflammatory lesions of a moderate degree (<i>hepatitis chronica activa mediocris gradus</i>)
4	periportal inflammatory infiltration, piecemeal necrosis of a high degree, coexistence of inflammatory lesions of a bridging type (portal-venous), widespread damage to hepatic cells (<i>hepatitis chronica activa maioris gradus</i>)

TABLE 2 The progression of fibrosis (S) in the liver, scored from 0 to 4 according to Batts-Ludwig¹⁷

0	none
1	fibrosis in portal areas
2	periportal fibrosis, presence of single septa (barriers) between neighboring portal areas
3	presence of fibrous septa connecting neighboring portal areas, and portal areas with a central lobular vein, initial distortion of the lobule architecture
4	cirrhosis – modeling of the liver and regenerative nodules present

symptoms and complications occur in about 20% of patients.⁸⁻¹²

Mortality among patients with liver cirrhosis induced by HCV infection – resulting from the development of portal hypertension, liver failure or primary liver cancer (HCC) – reaches 2–5% yearly, whereas the prevalence of HCC development is about 1–4% per year.^{1,3}

Diagnostics of HCV infection Once HCV was discovered (in 1989), and generations of tests appeared, the rate of infection through blood transfusions and organ transplants decreased. Before 1989, blood was considered a potentially contagious material (and a blood donor as a potentially infected person) when serum ALT levels were high. The 1st generation ELISA test introduced in May 1990 had a sensitivity of 46%, the 2nd generation ELISA test (July, 1991) was sensitive to 60%, the RIBA-II test (recombinant immunoblot assay II) increased its sensitivity to 90%. Studies performed in 1992 in the USA showed the risk of contracting HCV infection during a blood transfusion to be as high as 4%, whereas after introduction of the 2nd generation tests (ELISA, RIBA-II), it declined to 0.6%. The 3rd generation ELISA test is highly sensitive and its sensitivity exceeds 99%, and an additional assay of HCV-RNA by PCR technique further limits the chance of transfusion-mediated HCV infection.³

Recent diagnostic procedures for the detection of HCV involve application of 3rd generation ELISA tests, containing core antigens (C) and at least 2 antigens of non-structural proteins.

The sensitivity and specificity of these tests are approximately 99%. The presence of anti-HCV antibodies in serum alone is no evidence of HCV infection. The antibodies may be detected in those individuals who have a history of hepatitis C. Moreover, HCV infection may occur in immunosuppressive patients with no detectable anti-HCV antibodies. Another type of investigation that can confirm HCV which should be performed following the detection of anti-HCV antibodies in serum is the estimation of HCV genetic material in the blood. The RT-PCR assay (reverse transcription polymerase chain reaction) with a sensitivity of 98% is most commonly used. For a quantitative evaluation of the virus, which is essential for assessment of the anti-viral treatment effectiveness, branched DNA and PCR assays are used. These tests are able to evaluate the core HCV antigen (HCVAg), and are useful in diagnostic evaluation within the “serological window”, i.e. before anti-HCV antibodies are present.¹³⁻¹⁵ The earliest serological marker of the HCV infection is HCV-RNA, which can usually be detected 1–2 weeks after the onset of the infection. Then, with a delay of 1–1.5 days, HCVAg appears. Anti-HCV antibodies may be detected, on average, 3–8 weeks after contracting the infection, most commonly 34 days after the moment when HCV-RNA appears in the blood.³

Histological lesions in the liver Inflammatory infiltration, fibrosis and degeneration of hepatocytes represent histological lesions in the liver during the course of hepatitis C, both in its acute and chronic phase. Inflammatory infiltrations are located intralobularly and in the portal area, and consist of lymphocytes, plasmocytes and antigen-presenting cells. The degenerating cells are swollen, demonstrate acidophilic degenerative lesions, acidophilic particles or Councilman-like bodies. Approximately 50% of patients with hepatitis C display features of liver steatosis. Hepatocyte necrosis may be focal or confluent. When a confluent necrosis leads to a fusion of vascular structures of portal areas, it is described as a bridging necrosis. The topography of inflammatory and degenerative lesions of hepatocytes depends on the phase of inflammation; in an acute phase lobular lesions prevail, whereas in a chronic phase lesions in the portal areas are usually more common.

A histopathological presentation of the HCV infection is similar to the lesions occurring in the HBV infection. However, the damage to the bile duct system, formation of the lymph follicles in portal areas, focal macrovesicular steatosis (coarse droplets) and, occasionally, presence of Mallory’s bodies are more frequently reported in hepatic C.¹⁶ (TABLE 1, TABLE 2)

Treatment with interferon α and ribavirin Treatment of chronic hepatitis C viral infection is one of the most serious issues in contemporary medicine. The rate of patients with a spontaneous

TABLE 3 Adverse effects of interferon and ribavirin

Adverse effects of interferon
fever
flu-like symptoms
insomnia, sub-depressive episodes, depression
thyroid dysfunction
leucopenia, thrombocytopenia
alopecia
Adverse effects of ribavirin
hemolysis
increased plasma uric acid levels
cough
rash, itching

clearance of the virus in this disease is the lowest out of all forms of viral hepatitis. The course of chronic hepatitis C is usually rather slow, but it inevitably leads to severe complications, including liver cirrhosis and HCC. If the condition affects young individuals with a potentially long life expectancy, development of such complications is almost certain.

Currently, a combination of pegylated interferon α (PEG-IFN) and ribavirin over a period of 24–48 weeks is used in the treatment of chronic hepatitis C. Previously, a recombinant form of interferons was used, replaced finally by a recombinant PEG-IFN.

Introduction of pegylated interferons has improved the effectiveness of the therapy for HCV infection. PEG-IFN α is the interferon conjugated with polyethylene glycol with a long half-life and improved bioavailability. Due to the introduction of the polyethylene glycol molecule, the drug remains longer in the bloodstream and its blood level is more stable.^{3,18}

The effectiveness of treatment with interferon α and ribavirin reaches 37–42%, whereas that of PEG-IFN and ribavirin in patients with a non-1 genotype amounts to 78%, and to 55% in patients with a 1 genotype.^{3,19–23}

The adverse reactions of interferon and ribavirin are shown in [TABLE 3](#).^{1,3,4}

Inclusion criteria for patients with chronic hepatitis C to receive antiviral treatment has changed over the last few years. Initially, patients with chronic hepatitis C with the persistent elevated ALT activity for more than 6 months, compensated liver function, histological lesions in the liver (fibrosis, inflammation) and without contraindications were eligible to treatment. Such treatment lasted from 24 to 48 weeks, depending on the virus genotype, and was 40% effective. In recent years, the concept that the progress of the disease is very slow in patients with normal ALT activity has been challenged. Schiffman et al. have reported data regarding 480 patients with chronic hepatitis C exhibiting normal ALT activity and a lesser progression of lesions on histological examination than patients with high ALT activity combined with advanced necrotic and inflammatory lesions

and fibrosis. Schiffman et al. have claimed that patients with normal ALT activity should be treated using the same approach as those with increased ALT activity,²⁴ which has been widely approved in the current therapeutic recommendations.

Important data have been presented by Prati et al. who have shown that patients with normal ALT activity, treated with PEG-IFN and ribavirin, achieve SVR (sustained virological response) and exhibit a further decrease in ALT activity. The authors suggest that the upper limit of the reference range for ALT should be revised.²⁵

At present, the American Association for the Study of Liver Diseases recommends the following approach in the evaluation of patients with chronic hepatitis C who qualify for antiviral therapy. The patients are assigned to 3 groups. The first 2 groups involve patients with clear indications or contraindications. The 3rd group consists of the patients with no definite signs required to introduce treatment, and who should be evaluated on an individual basis. Patients with the confirmed presence of virus genetic material (positive HCV-RNA) are selected for the treatment. Recommendations are presented in [TABLES 4, 5 and 6](#).²⁶

The purpose of the HCV infection treatment is the permanent inhibition of virus replication, arresting or slowing the progress of histological lesions in the liver, and the biochemical normalization of liver function parameters. Nucleotide sequence variability observed in particular genotypes and subtypes of virus has a serious impact on the response to treatment. Genotype 1 and 4 are less susceptible to treatment. This variability makes the development of a vaccine difficult.^{27,28}

In the recent years, promising attempts have been made to treat acute hepatitis C. It turned out that the effectiveness of therapy with interferon α in this group of patients is higher than in those with interferon and ribavirin in patients with chronic hepatitis C. Sustained virall response in patients with acute hepatitis C treated with interferon α amounts to approximately to 70–95%. At the same time, there are insufficient data to assess which patients should be treated, in what period of time the antiviral therapy should be introduced and how long the therapy should be conducted. Given the preliminary data, it appears that the therapy should be delayed by about 12 weeks from the onset of symptoms. At that time approximately 15–20% of patients spontaneously eliminate the virus. Available meta-analyses show that the 2–3-month delay in therapy has no negative impact on SVR. It also seems that the inclusion of ribavirin into the regimen does not improve SVR.^{29–31}

After antiviral treatment, patients should still be taken care of by the Viral Hepatitis Out-Patient Clinic. In those patients who have not presented SVR, the liver function tests, α -fetoproteins and the USG of the abdomen should be performed every 6–12 months. Furthermore, another course

TABLE 4 Characteristics of patients for whom the enrollment criteria of the treatment are widely accepted

Age: ≥18 years
Abnormal alanine aminotransferase activity
Features of chronic hepatitis C with significant fibrosis in the liver biopsy
Compensated liver injury (bilirubin <1.5 g/dl, INR <1.5; albumin >3.4 g/dl, platelet count >75,000/mm ³ , no encephalopathy, no ascites)
Hemoglobin >13 g/dl in men and >12 g/dl in women; neutrophil count >1500/mm ³ , creatinine <1.5 mg/dl
Previous treatment with antiviral drugs
Well controlled depression is not a contraindication
No absolute contraindications

Abbreviations: INR – international normalized ratio

TABLE 5 Characteristics of patients with absolute contraindications for enrollment in the therapy

Uncontrolled depression
Patients who have had kidney, heart or lung transplants
Autoimmune diseases or other diseases aggravated by interferon and ribavirin
Untreated hyperthyroidism
Pregnancy or inability to use adequate contraception
Improperly treated or severe cardiac diseases, incl. severe hypertension, circulatory failure, ischemic heart disease
Uncontrolled diabetes or chronic obstructive lung disease
Age <3 years
Hypersensitivity to interferon or ribavirin
Drug addiction

TABLE 6 Characteristics of patients in whose case the decision for the approval of treatment should be made on an individual basis

Sustained normal alanine aminotransferase activity
Drug-addicts, alcoholics willing to start detoxification treatment
No fibrosis or mild fibrosis in biopsy
Age <18 years
Chronic kidney disease
Decompensated liver cirrhosis
Patients following liver transplant

of therapy with PEG-INF and ribavirin should be considered, and patients should be given additional antiviral therapy in the advent of new, more effective antiviral drugs. Patients with SVR should receive ongoing check-ups from the Viral Hepatitis Out-Patient Clinic every 1–2 years. These patients should be under a careful supervision in case they develop immune disorders or a condition that requires immunosuppressive treatment.

Measures taken after exposure to HCV HCV infection may be an occupational hazard, especially for health care providers, but also for policemen, city police and penitentiary service workers. The highest risk of a transmission of the infection

is observed after accidental injury with a needle or other sharp device stained with HCV infected blood – this amounts to approximately 1.8%. The risk of the infection from the mucosa's contact with a HCV-positive patient's blood is very low, and, as yet, there are no reports on the transmission of HCV infection by spills on the skin. The basic technique used for prevention of HCV infections (and also HBV, HIV) in professional practice is proper staff training. Employers should provide health care workers with ongoing access to a doctor. Each staff member should immediately report exposure to contagious material to a designated doctor, who will evaluate the risk of having contracted HCV infection and undertake the adequate procedure. Wounds and skin contaminated with a contagious material should be washed with soap and water, while the mucosa can be just rinsed with water. There is no evidence confirming antiseptic agents to be more effective, though they are not contraindicated. There is no reliable data pointing to the effectiveness of immunoglobulins in post-exposure practice. Available data show that interferon is only effective for full-blown hepatitis C. Base-line serum anti-HCV antibodies and ALT activity in an exposed person should be determined, and, in the event of the absence of HCV antibodies, the tests should be repeated after 6 weeks, and then after 3 and 6 months.^{32,33}

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